Synthesis and biological activity of novel quinoxaline 1,4-dioxide derivatives

Abstract

The chemistry of *N*-oxides of heterocyclic compounds is one of the dynamically developing areas of organic synthesis. The synthetic potential of quinoxaline 1,4-dioxides determines the prospects of their use for the purposeful design of compounds with practically valuable properties, and also the relevance of this study and its scientific significance. Quinoxalin 1,4-dioxides are also promising platform for the developing new drugs against tuberculosis and parasitic infections such as malaria, trypanosomiasis, leishmaniasis, amoebiasis, and trichomoniasis. Some derivatives are patented as antimicrobials and are used in agriculture as bactericides and promoters to increase animal weight gain. Thus, further study of the chemical properties of this class of compounds and the study of the role of structural fragments in the biological properties of such derivatives is advisable for the creation of new drugs with improved pharmacological properties.

The main goals of the present work are the development of new directions of chemical modification of quinoxaline 1,4-dioxides, promising for obtaining polyfunctional biologically active compounds, **the following objectives have been proposed**:

1. The study of the interaction of monosubstituted benzofuroxans with CH-acids; the study of the reactions of halogenated quinoxaline 1,4-dioxides with diamines; development and optimization of methods for the chemical transformation of quinoxaline 1,4-dioxides containing substituents in positions 2, 3, 6 and 7 of the heterocyclic ring; synthesis of derivatives with acceptable solubility in aqueous media.

2. An evaluation of the antimicrobial properties of quinoxaline 1,4-dioxides against a wide range of pathogens, as well as antiproliferative activity in a panel of cancer cells, including MDR cell lines.

3. Revealing the role of individual structural fragments in the ability of quinoxaline 1,4-dioxides to induce the death of cancer, bacterial or protist cells.

Scientific novelty

1. A study of the regioselectivity of the Beirut reaction between monosubstituted benzofuroxans and benzoylacetonitrile showed that in the case of benzofuroxans with

electron-withdrawing substituents, a mixture of 7(6)-substituted quinoxaline-2-carbonitrile 1,4-dioxides is formed, and the proportion of 6-substituted isomers increases with increasing electron-withdrawing effect deputy. A series of previously undescribed 6-substituted 3-phenylquinoxaline-2-carbonitrile 1,4-dioxides has been obtained and characterized.

2. An original approach to the synthesis of 7-amino derivatives of 6-haloquinoxaline 1,4-dioxides has been developed, for the irealization of which a preparative scheme for the synthesis of 5-aminobenzofuroxans has been created. The regioselectivity of heterocyclization of 5-amino derivatives of benzofuroxan with benzoylacetonitrile and 1-acyl-3,3,3-trifluoroacetones, leading to the formation of 7-amino-substituted products, was revealed.

3. A high regiospecificity of nucleophilic aromatic substitution of halogen atoms by cyclic diamines in position 6 and/or 7 of 6,7-dihalo-substituted quinoxaline 1,4-dioxides with different electronic effects of substituents in position 2 and 3 of the heterocycle was found.

4. A series of 6(7)-amino derivatives of quinoxaline 1,4-dioxide was synthesized, with a variation of substituents in position 2, 3, 6 and 7 of the heterocyclic ring, which have high solubility in pharmacologically acceptable aqueous media.

5. More than 50 derivatives have been obtained that inhibit the growth of tumor and bacterial cells. Derivatives that overcome the mechanisms of drug resistance in tumor cells associated with the excretion of chemotherapeutic agents by the P-gp transmembrane efflux pump and deletion of the p53 suppressor gene have been identified. The role of individual structural fragments and their location in the quinoxaline core in the biological properties of the obtained derivatives was studied, which makes it possible to modulate the spectrum of activity of such compounds and the effect on hypoxic signaling pathways in tumor cells.

6. It was found that for a number of derivatives their selective hypoxic cytotoxicity is due to the ability to inhibit the expression and activity of the hypoxia-induced factor HIF-1α, causing apoptosis in tumor cells under hypoxic conditions. It has been shown for the first time that apoptosis of tumor cells is induced by quinoxaline-2-carbonitrile 1,4-dioxide derivatives by a p53 independent mechanism.

Practical significance

consists in the development of schemes for the synthesis of a series of biologically active derivatives of quinoxaline 1,4-dioxide, as well as the methods of heterocyclization of monosubstituted benzofuroxans, the chemical properties of some derivatives of quinoxaline 1,4-dioxide, the schemes for their preparation and the possibility of their chemical modification. The data on the "structure-activity" relationship revealed in the study, as well as the structural features of pharmacophore groups that are important for the manifestation of biological activity will contribute to the further development of the targeted synthesis of chemotherapeutic agents. A number of compounds have been found that have a high antitumor potential, most of which have selective cytotoxicity against malignant cells under hypoxic conditions, as well as high activity against resistant tumor cells with MDR. Leading compounds with improved pharmacological properties were selected for further in-depth preclinical studies.

Theses to be sustained

• Regioselectivity of the reaction of monosubstituted benzofuroxans with benzoylacetonitrile and 1-acyl-3,3,3-trifluoroacetones, leading to the formation of a mixture of isomeric products, the ratio of which, to a greater extent, depends on the electronic effects of benzofuroxan substituents; proof of the structure of the resulting isomers;

• Regiospecific substitution of halogen atoms in position 6 and/or 7 in 6,7-dihalo-substituted quinoxaline 1,4-dioxides with variation of substituents in positions 2 and 3 of the heterocyclic nucleus with amines; the results of a study of the physicochemical and spectral characteristics of such derivatives;

• Development of a method for the synthesis of 7-amino derivatives of 6-haloquinoxaline-2-carbonitrile 1,4-dioxides. Selectivity of the Beirut reaction between 5-amino derivatives of benzofuroxans and benzoylacetonitrile, as well as 1-acyl-3,3,3-trifluoroacetones, leading to the formation of 7-amino derivatives of 6-haloquinoxaline 1,4-dioxides;

• Results of screening of biological activity of new derivatives of quinoxaline 1,4-dioxide and their effect on intracellular targets; analysis of regularities between the structure of the obtained compounds and their biological activity.